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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,055	09/05/2003	Debbie Yaver	10322.200-US	8946
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NOVOZYMES, INC. 1445 DREW AVE DAVIS, CA 95618			EXAMINER HINES, JANA A	
			ART UNIT	PAPER NUMBER
			1645	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Patents-US-CA@novozymes.com

Office Action Summary

Application No.

10/656,055

Applicant(s)

YAYER ET AL.

Examiner

JaNa Hines

Art Unit

1645

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 11, 36, 42, 43, 82-88 and 90-96 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 11, 36, 42, 43, 82-88 and 90-96 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Amendment Entry

1. The amendment filed December 28, 2009. Claims 2-10, 12-35, 37-41, 44-81 and 89 are cancelled. Claims 94-96 are newly added. Claims 1, 11, 36, 42-43, 82-88 and 90-96 are under consideration in this office action.

Response to Arguments

2. Applicant's arguments filed December 28, 2009 have been fully considered but they are not persuasive.

Previous Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 1, 11, 36, 42-43, 82-88 and 90-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wilson et al., (PNAS, 1999. Vol. 96(22): 12833-12838) in view of Cao et al., (Mol. Microbio. 2002. Vol. 45(5): 1267-1276).

The rejection was on the grounds that it would have been *prima facie* obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain used in DNA

hybridization microarrays of Cao et al., to Wilson et al., method for determining the mode of action of an antimicrobial compound comprising detecting hybridization complexes and assigning a mode of action in order to provide obtain antimicrobial mode of action results for *B. subtilis* which is known to be resistant to known antimicrobial drugs.

Response to Arguments

4. Applicant's arguments filed December 28, 2009 have been fully considered but they are not persuasive.

Applicants point to a definition of subinhibitory amount within the instant specification at Pages 11-12, lines 35-3. Applicants note that the Office Action of September 25, 2007 withdrew the 35 USC 112 2nd rejection in view of applicants amendments and arguments.

Applicants point to the Office Action of June 25, 2009 which states "it would appear that subinhibitory means an amount that is not able to kill the bacteria". Then Applicants states that the record and the specification are contrary to this statement by the Office, as stated above. The specification states on page 11, lines 3-5: "MIC is defined as that concentration of an antimicrobial compound resulting in no visible growth of the organism". Consequently, the MIC results in no growth. Subinhibitory concentrations would result in growth. " The Office agrees with Applicant, as previously stated in the last Office Action subinhibitory means an amount that is not able to kill the bacteria, i.e., would result in growth.

Applicants asserts that Wilson *et al.*, does not teach the subinhibitory amount limitation because Wilson *et al.*, *Mycobacterium tuberculosis* to isoniazid (INH) at concentrations of 0.2 ug or 1 lug of INH per ml, which are above the minimum inhibitory concentration of INH, *i.e.*, 0.02 ug of INH per ml. First, 0.02 ug of INH merely respects an example of a subinhibitory amount, and does not limit the claims. Therefore, the fact that Wilson *et al.*, teach other amounts of INH, which also do not kill the bacteria means that Wilson *et al.*, meets the limitation of the claims. Contrary to Applicants' assertion, Wilson *et al.*, teach amounts that result in bacterial growth. As Applicants have already stated, the subinhibitory amounts would be amount below the minimum inhibitory concentration, would not kill the bacteria and show signs of growth. Wilson *et al.*, teach concentrations of 0.2 ug or 1 lug of INH per ml, growth occurs and the bacteria is not killed as evidenced by the INH-induced expression profiles. Thus, Wilson *et al.*, meets the sub-inhibitory limitation of the claims.

Applicants assert that the Schaaf *et al.*, was printed after the priority date of the instant application. Applicants also state that Schaaf *et al.*, disclose isoniazid-resistant mutants which are different than the teachings of Wilson *et al.* it is noted that Schaaf *et al.*, was merely used as evidence concerning the subinhibitory amount of INH. With respect to the actual claims of record, Wilson *et al.*, teach concentrations of 0.2 ug or 1 ug of INH per ml, which are below the minimum inhibitory concentration of INH, *i.e.*, 0.02 ug of INH per ml; thereby using concentrations that result in growth, while also meeting the limitations of the claims.

Applicants argue that the teachings of Wilson are incorrect and not supported by the record. Below is a detailed teaching of the instant claims and prior art teaching.

The claims are drawn to a method for determining the mode of action of an antimicrobial compound. Wilson et al., teach exploring drug (the antimicrobial compound) induced alterations in gene expression in *Mycobacterium tuberculosis* by microarray hybridization (title). Wilson et al., conclude the observation that the INH response profiles were distinct from profiles obtained from bacteria exposed in a similar manner to a variety of different toxic compounds, including hydrogen peroxide, ethanol, and aminoglycoside antibiotics (page 12,838). Cao et al., teach comparing *M. tuberculosis* to various antibiotics (page 1273, col.1).

The claims recite detecting hybridization complexes formed by contacting at least one nucleic acid sample, in the presence of at least one subinhibitory amount of an antimicrobial compound. Wilson et al., teach growth and drug treatment of bacterial *M. tuberculosis* strains wherein cultures were treated with 0.2ug/ml or 1.0ug/ml for INH (page 12384). Wilson et al., teach techniques for microarray hybridization and data analysis at page 12,385, see also Figure 2 showing INH-induced mRNA expression profiles monitored by microarray hybridization analysis (page 12,285). Cao et al., teach detecting hybridization complexes formed by contacting at least one nucleic acid sample (page 1274, col. 2).

The claims recite obtained by culturing bacterial cells in the presence of at least one subinhibitory amount of an antimicrobial compound having an unknown mode of action. Wilson et al., teach culturing, growth and drug treatment of the bacterial strains

with the drug (page 12,834). Cao et al., teach culturing *B. subtilis* strains for DNA microarray analysis (page 1274, col. 2).

The claims recite using a plurality of nucleic acid sequence corresponding to genes of the bacterial cells. Wilson et al., teach the preparation of DNA microarrays which contains genomic sequences and fragments on a substrate (page 12,834). Cao et al., teach using a plurality of nucleic acid sequence corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate (page 1274, col. 2).

The claims recite wherein the plurality of nucleic acid sequences is contained on a substrate, wherein the presence, absence or change in the amount of the hybridization complexes detected. Wilson et al., teach microarray hybridization where the DNA was applied to the array in a hybridization mixture containing genomic sequences and fragments thereby allowing hybridization to occur (page 12,835). Cao et al., teach the plurality of nucleic acid sequences is contained on a substrate (page 1274, col. 2).

The claims recite comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the bacterial cells cultured in the absence or presence of a standard compound having a known mode action. Wilson et al., teach that this system provides the framework for interpreting the transcriptional responses that we would detect by the microarray hybridization and allow for comparison with published results of genes and proteins that are known to be INH induced (page 12,833). Wilson et al., teach the results show that

the characteristic drug response is the result of intracellular conditions associated with the drugs mode of action (page 12,838). Cao et al., teach detecting and quantifying the presence, absence or change in the amount of the hybridization complexes, and comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode action, is indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound using data analysis software (page 1274, col.2).

The claims recite presence or absence of the compound being indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound. Wilson et al., teach the detection of hybridization complexes formed by contacting at least one nucleic acid with a plurality of nucleic acid sequences corresponding to genes of the bacterial cells (page 12,835). Cao et al., teach comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells as indicative of the similarity or dissimilarity of the mode of actions of the antimicrobial compound and the standard compound using data analysis software (page 1274, col.2).

Thus, the argument that the rejections of record are not supported by the prior art reference is not found persuasive.

Applicants write that Wilson et al., teach concentration that are above the MIC. In order for the cultures to result in growth and not die, the concentrations must be above

the MIC. It is agreed that Wilson et al., teach concentrations above the Minimum Inhibitory Concentration amount. Moreover, all of the claims require that the concentration be above the MIC amount, in order to assign a mode of action for that antimicrobial compound.

In response to applicant's argument that there is no suggestion to combine the Wilson et al., and Cao et al., references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In this case, it is noted that Wilson et al., do not teach culturing cells of *Bacillus subtilis*. Cao et al., teach culturing *B. subtilis* strains for DNA microarray analysis (page 1274, col. 2). Cao et al., teach detecting hybridization complexes formed by contacting at least one nucleic acid sample, obtained by culturing *Bacillus subtilis* cells in the presence of at least one subinhibitory amount of an antimicrobial compound having an unknown mode of action, with a plurality of nucleic acid sequence corresponding to genes of the *Bacillus subtilis* cells, wherein the plurality of nucleic acid sequences is contained on a substrate (page 1274, col. 2). Cao et al., teach detecting and quantifying the presence, absence or change in the amount of the hybridization complexes, and comparing with hybridization complexes formed between the plurality of nucleic acid sequences and a second nucleic acid sample obtained from the *Bacillus subtilis* cells cultured in the absence or presence of a standard compound having a known mode action, is indicative of the similarity or dissimilarity of the mode of

actions of the antimicrobial compound and the standard compound using data analysis software (page 1274, col.2). Cao et al., teach comparing *M. tuberculosis* to various antibiotics (page 1273, col.1). Cao et al., teach that *B. subtilis* co-exists with many microorganisms and that Bacillus' antibiotic resistance genes need control (page 1267, col.2).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply the *Bacillus subtilis* strain of Cao et al., to Wilson et al., method for determining the mode of action of an antimicrobial compound in order to provide obtain antimicrobial mode of action results for *B. subtilis* which is known to be resistant to known antimicrobial drugs.

With respect to Applicants argument that the inventive concept is drawn to the use of subinhibitory amounts; it is the Office's position that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case, the prior art sets forth the use of subinhibitory amounts when detecting hybridization complexes; therefore Applicants use of a workable range of subinhibitory amounts is not fund persuasive to overcome the prior art rejection. See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.").

Applicants argue that Wilson et al., in view of Cao et al., teach away from using subinhibitory amounts of an antimicrobial compound. In response, disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). However, "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). It is the position of the Office that that applicant's argument that the reference teaches away from using subinhibitory amounts was insufficient to overcome the rejection since Applicants still have not asserted discovery beyond what was known in the art.

Wilson et al., clearly and specifically teach the growth and drug treatment of the strain wherein cultures grown and treated with 0.2ug/ml or 1ug/ml the antimicrobial compound which meet the limitations of subinhibitory amounts contrary to Applicants' assertions. Therefore contrary to applicants' argument, the prior art does not teach away from the instant claims.

Therefore Applicants' argument is not persuasive and the rejection is maintained.

Conclusion

5. No claims allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/
Primary Examiner, Art Unit 1645